REMARKS

Reconsideration is respectfully requested in view of the foregoing amendments and the remarks which follow.

Claim 1 has been amended by specifying that both components (i) and (ii), i.e. the active principle and the synergist component, are jointly complexed with a cyclodextrin. This amendment is supported at page 2, lines 30-32 and at page 5, lines 15-17. The formation of the CD_complex with both the active principle and the synergistic component is also confirmed by the NMR study filed before the International Preliminary Examination Authority as Annex 2, copy of which is attached hereto and commented upon hereafter.

Claim Rejections under 35 USC § 112

In the outstanding Office Action, the Examiner rejected claim 9 under 35USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention.

Claim 9 has now been amended by deleting the term "possibly" and thus overcoming rejection. Withdrawal of the § 112 rejection is solicited.

Claim Rejections under 35 USC § 102

Claims 1-9 have been rejected under 35 USC 102(b) as being anticipated by Biebel et al. This rejection is traversed.

Biebel et al disclose compositions where cyclodextrin is complexed with an insecticide **OR** with a synergistic compound. There are no compositions disclosed where the complex is based on a **cyclodextrin complex which is made by both the active ingredient and the synergistic compound.**

During International Preliminary Examination, Applicants demonstrated by the filing of Annex 2 that the composition of the claimed invention comprises a cyclodextrin complex with the ***simultaneous presence*** of an active ingredient as in subparagraph (i) of claim 1 and the synergistic compound as in subparagraph (ii) of claim 1.

Annex 2 is attached hereto in order to also be taken into consideration by the Examiner. The annexed NMR data of pyrethroids and cyclodextrins in the absence and in the presence of a synergistic compound as PBO shows the joint complexation as per claim 1. Evidence of the complexation obtained by the Applicants is shown in these spectroscopic data where, according to what is known in the literature for NMR spectra of cyclodextrin complexes, the shifts of the relevant protons are observed.

Furthermore, these data demonstrate that the complexes of the invention are ***not*** a ***physical mixture of the three components***. This is a clear difference which distinguishes over the Biebel et al. disclosure.

In order to optimize efficacy, Biebel et al. teach to regulate the dosage of the agents (page 177, right column, lines 9-11 and "conclusions" on page 180). However, the regulation of dosages has absolutely nothing whatever to do with the solution adopted by the claimed invention.

Complexation is not used in Biebel et al to increase the activity of the treatment. Rather, it is used to protect the photolabile pyrethroid component from degradation when exposed to the light (see abstract, first four lines and page 180, left column, lines 19-22). The foregoing extract from Biebel et al. most certainly does not suggest complexing PBO or sesamol as stated by the Examiner, since they are not photolabile substances.

When discussing biovailability issues, Biebel at al. teach that the ***complexation*** of the synergistic agent in cyclodextrin is an ***obstacle*** to its delivery in vivo (see page 179, left column, last four lines). Thus, one of ordinary skill in the art would have been ***taught away by Biebel et al.*** from including the synergistic compound in the cyclodextrin, since Biedel's clear teaching is to ***separate the synergist from the cyclodextrin***.

Furthermore, the complex of pyrethrum prepared in Biebel at al. with PBO as synergist, has only a slightly enhanced action compared to a commercial product containing pyrethrum in its free form (see abstract of Biebel et al.). By contrast, complexes with many insecticides (pyrethroids) prepared in accordance with the claimed invention are always much more efficient as reported in the specification (see page 3, first paragraph-page 5, lines 18-26) and exemplified in biological assays in comparison with all the commercial products, even when the concentration of both components,

insecticide (pyrethroid) and synergist, is lower than the optimal concentration found in Biebel et al. In addition, the claimed complexes have been found to be more active than the mixtures of the two agents.

Surprisingly and unexpectedly, the joint complexation of the active ingredient and the synergist of the claimed composition, did not result in a lesser bioavailability of the synergist as feared from Biebel et al.'s teaching, nor did it result in an equal delayed release for the two agents.

Applicants by virtue of the NMR spectroscopic data analysis (see Annex 2) found that the pyrethroid begins to be delivered by the complex only after some hours. By contrast, more than 90% of PBO is released by the complex very quickly when it is dissolved/suspended in water, thereby maximizing the synergistic effect. The earlier release of the PBO inhibits the detoxication enzymes of the insect. The later-released pyrethroid acts on the PBO pre-sensitised insect.

In view of the foregoing, the claimed invention clearly distinguishes over the teaching of Biebel et al. by a preponderance of the evidence. Since the Examiner has not presented a *prima facie* case under § 102(b), withdrawal of the rejection is solicited.

Claims 1-9 stand rejected under 35 USC § 102(b) as being anticipated by Mifune et al. (US 3,846,551). This rejection is traversed.

The Examiner states that Mifune et al. "*disclose examples wherein a pyrethroid, cyclodextrin and piperonyl are well kneaded to form a paste (formulation example 7).... Therefore, the compositions according to Formulation Example 7 would comprise both the pyrethroid and the synergist complexed with cyclodextrin since they were well kneaded in the presence of cyclodextrin in water.*"

Applicants strongly traverse the reasoning of the Examiner for the following reasons.

As clearly stated in the instant specification at page 2, lines 11-13 "*US 3,846,551 states that the activity of the insecticides complexed with CD is better than that of uncomplexed insecticides. However, formulations also containing simultaneously a synergistic compound have never been described.*" As a matter of fact, Mifube et al.

describe the complexation between the insecticide and a cyclodextrin, but nowhere is joint complexation also with a synergistic compound disclosed.

When read correctly, Formulation Example 7 of Mifune et al. states that the preformed interacted compound of insecticide and beta-cyclodextrin is mixed with piperonyl butoxide, stearic acid and Tween 60. The complex therefore which is already formed is made by the insecticide and the cyclodextrin as, without doubt, is stated throughout the Mifune et al. description. Following the reasoning of the Examiner, according to Formulation Example 7, a complex with stearic acid can also be formed as well as with Tween 60, without excluding the possibility of the insecticide being absent from the complex and the presence of PBO in the complex, with or without stearic acid.

However, there is absolutely no disclosure of the formed complex of ***BOTH*** the active ingredient ***AND*** the synergist compound present in Mifune et al, other than by an ex-post facto analysis, i.e., from knowledge of the present invention, as applied by the Examiner. Such 20/20 hindsight reasoning based on Applicants's own disclosure is clearly improper.

Therefore, claims 1-9 distinguish over the teaching of Mifune et al. Since the Examiner has failed to establish a ***prima facie*** case of anticipation, the rejection has been overcome and its withdrawal is solicited.

Claims 1,2, 5, 8 and 9 stand rejected under 35 USC 102(b) as being anticipated by Szejtli et al. (US 4,524,068). This rejection is traversed.

Szejtli et al. describe a complex of PBO with CD which is more effective than the uncomplexed PBO. There is no disclosure of the formed complex of ***BOTH*** the active ingredient ***AND*** the synergist compound present in Szejtli et al.

In view of the amendment to claim 1, clearly specifying that the active ingredient and the synergist are jointly complexed in a cyclodextrin, this rejection has been overcome since the claim distinguishes over the reference. Withdrawal of this § 102 (b) rejection is respectfully requested since ***prima facie*** anticipation has not been established.

During International preliminary Examination Annex 1 was filed to further support the activity of the composition of the present invention. Annex 1 is submitted

herewith to be taken into consideration by the Examiner in evaluating the patentability of claim 1.

CONCLUSION

In view of the foregoing, Applicants believe that the Restriction Requirement should be withdrawn, and that the currently pending claims are in condition for allowance on the grounds that the amendments to the claims fully overcome the rejections set forth in the outstanding Office Action.

Accordingly, Applicants respectfully solicit the issuance of a Notice of Allowance.

Please charge any fees which may be due and which have not been included herewith to our Deposit Account No. 01-0035.

Respectfully submitted,

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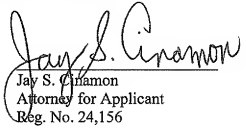
By 
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